Informed diuretic choices in the ICU

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This chapter is relevant to the aims of Section H3(i) from the 2023 CICM Primary Syllabus, which expects the exam candidate to *"understand the pharmacology of diuretics"*; where *"understand"* is being interpreted more generally as *"grasp the nature and significance"* or *"apprehend clearly the character, nature, and subtleties"*. Having written this, the author must be clear that he does not claim to apprehend the character or subtleties of anything, and learned an embarrassing amount of new information in the process of creating this summary. And if the chapter contains practical information that is new for a grown-ass intensivist, then it probably belongs more in the Second Part section. The main objective here was to review the scientific rationale for the diuretic-related decisions we make in the ICU, or at least to expose naked patches of superstition when there's none. No CICM exam question has ever touched on this, but one can conceive of some terrible future where the candidates are asked to "discuss the factors that affect the choice of diuretics in a critically ill patient" or somesuch.

In summary:

- **Loop diuretics are first-line:**
  - There little to discriminate between them as a class
  - An infusion may be better haemodynamically tolerated and more titratable, with reduced risk of toxicity
  - Treatment failure should be followed by monotherapy dose escalation up to a maximum of perhaps 160-200mg/day
  - Vexatious side effects or failure of this high dose should prompt the addition of a second agent
- **The second agent should be amiloride or spironolactone**
  - Amiloride is faster acting but renally cleared
  - Spironolactone is a better choice for long term management
  - The enhancement of diuresis with these is limited, but they permit higher doses of loop diuretics to be used
- **If the diuresis is inadequate, or hypernatremia develops, the third second agent should be a thiazide**
  - Thiazides have a synergistic natriuretic effect with loop diuretics, thus restoring normal sodium levels and increasing the total volume removal

- **If the diuresis is adequate but alkalosis develops, acetazolamide can be added; ... but:**
  - The diuretic effect is modest, and the impact of alkalosis is trivial, so this is rarely necessary
- **SGLT2 inhibitors and hypertonic saline are last-line medical therapies**
  - Both increase the effectiveness of loop diuretics but neither is a part of mainstream ICU practice
- **Medically refractory fluid overload is an indication for dialysis**
  - The safety and efficacy profile of ultrafiltration is similar to diuretic therapy, but the invasiveness puts it at the end of the list of options.

Probably the best narrative reviews of this deep ICU lore are Bissell et al (2020) and Frățilă et al (2023), and the best explanations of the different diuretic synergies can be found in Wilcox et al (2020). As peer-reviewed authors, of course none would have put their reputation on the line by making prescriptive recommendations for the use of diuretics in ICU.

A loop diuretic is usually the first line

Because they are safe and effective. Consider: chances are, the reason you are contemplating diuretic choices is because the patient needs to offload some fluid; and because we are discussing ICU patients, it is likely that you need to offload a large amount of fluid quickly. Of the diuretic classes, none has a safety/efficacy ratio that could compare to loop diuretics.

But one also needs to understand that efficacy in terms of litres of urine per dose is not the only characteristic worth considering. If it was, we would be giving people tens of grams of intravenous mannitol, and celebrating the torrential diuresis that ensues. Obviously this is not the best tactic for ICU patients, who may be hemodynamically fragile and who may not tolerate either the fluid shifts or the electrolyte derangement. On the other hand, one does not have days to wait - a decent diuresis needs to happen immediately. A large man with severe right heart failure might be carrying 20-30 litres of extra water, and he'd be growing breasts by the time you get this sort of negative balance with spironolactone. Loop diuretics occupy this perfect position in the Venn overlap of volume movement, haemodynamic tolerability, immediacy of effect, and side effects (of which the most noxious are easily corrected with electrolyte repletion).

This is not just some kind of deep ICU lore, it is genuinely based on some formal recommendation from the scientific establishment. Specifically, loop diuretics are

recommended as first-line for "congestion" in the 2022 AHA/ACC/HFSA guidelines as well as the 2021 ESC Guidelines. Yes, these are not ICU-specific guidelines, but they are written by people who run ICUs in countries with open ICUs, on the basis of trials performed largely on ICU-level patients, which should consolidate their credibility in the mind of the Australian reader.

But what of deep ICU lore? What are the wisened shamans of critical care doing in Australia? In 2015, Jones et al (2015) reported that the most popular choice among the locals was a 40mg bolus of IV frusemide. Similar numbers (94% frusemide) came from a survey of Americans, and internationally (98% frusemide). But why?

Is there no other loop diuretic than frusemide?

Yes, there are other loop diuretics. That class is not limited to frusemide and contains such members as torsemide, bumetanide, asozemide, piretanide, and ethacrynic acid. If the reader finds these names unfamiliar, this is not necessarily because the drugs themselves are at fault, as most of them have similar effectiveness and toxicity to frusemide. Most experts, when pushed to the wall, will admit that the main reason for the widespread use of frusemide is mostly cultural - it was developed earlier than the other agents and therefore became established before the others came along. And then frusemide became difficult to displace mostly because none of the other agents have sufficiently positive features to justify their selective use over frusemide. Still, some have weird superpowers that might make them more suitable for specific niche applications.

- **Ethacrynic acid** does not contain a sulfonamide substituent and is therefore tolerated by patients who have a "sulfa" allergy. The oral formulation causes diarrhoea, and the IV formulation causes a (mostly) reversible hearing loss, which seems to be a fairly reliable side effect. On the positive side, it acts as a venodilator, which could be helpful in acute pulmonary oedema.
- **Torsemide** has a reliable bioavailability of (80-90%) and this does not seem to vary overmuch, which is much better than frusemide. It also has a longer duration of action. This could be a valid choice where erratic gut absorption is suspected to be the reason for diuretic treatment failure. It also seems to block aldosterone receptors, which is handy because that is exactly the effect you want in the long term to prevent LV remodelling.

It is therefore surprising that you do not see it more often (it seems like the logical choice for long-term oral therapy), and some (eg. Buggey et al, 2015) suggest that it is severely underrated.

- **Bumetanide** is partly eliminated by hepatic metabolism, and is more bioavailable than frusemide. Though there are no guidelines directing this, it appears British physicians tend to prescribe it for more severely ill patients, which makes it look like it is associated with a higher mortality. It does not rely on tubular secretion, because it is sufficiently lipid-soluble that it can diffuse passively to the tubular apical membrane, unlike frusemide which needs to get into the tubular fluid first. One might think that this makes it a better choice in situations where the renal function is so poor that the urine output is basically zero. A retrospective audit of some neonate data suggests that this might be correct, as the chart review revealed the NICU intensivists would trial frusemide first, and then start bumetanide when they saw no response, with salutary effects.
- **Azosemide** seems like a safe alternative; it has poorer oral availability than any of the others (20% or so) and similar potency to frusemide (i.e. the IV dose is the same). Its duration of action is longer, which might be an advantage in the chronic management of heart failure, where counterproductive cardiac sympathetic nerve activity and RAAS tend to be over-excited by short acting diuretics. Matsuo et al (2016) suggested that azosemide might be a better choice of agent for this reason.

A review of the evidence by Wargo & Banta (2009) suggests that we should probably consider some of these alternatives more often. The usual dose equivalence for a 40mg dose of IV frusemide is 20mg of torsemide, about 0.75mg of bumetanide, or 50mg of ethacrynic acid, in case anyone wants to use these.

When should I switch to an infusion?

What might be the advantages of giving this agent by a continuous infusion, one might wonder. Several possible reasons can be advanced, such as:

- Less abrupt diuresis should be more "haemodynamically gentle" than bolus dosing
- Fewer high peaks of drug concentration, and therefore less ototoxicity (which means that one may be able to use huge total doses with less concern about deafness and tinnitus)

- Titratable, i.e. can be regulated to achieve the desired rate of diuresis

Weng et al (2023) looked at about 800 patients from the MIMIC-III database and determined that this strategy does indeed seem to get you more urine per milligram of frusemide, but only by about 230 ml per day in total. Sadly, the overall trend of the data appears to be in the direction of "no difference" as soon as one looks at meaningful metrics like mortality length of stay and progression to dialysis (Ng & Yap, 2018), perhaps because there is more to surviving an episode of acute heart failure than simply producing the largest amount of extremely dilute urine. This is in fact consistent with the findings of numerous trials that failed to produce a mortality benefit from diuretics alone, and with the recommendations of bodies such as the AHA, whose main focus is on the use of other GDMT elements. And that's only heart failure. Active deresuscitation is not a strategy that has ever been demonstrated to achieve its goals - for example, Messmer et al (2023) performed a meta-analysis of thrteen trials and concluded that none of the patient-centred outcomes were affected.

So, how much deresuscitation is enough?

How much urine do you seriously need?

The reader is reminded that their critically ill patient likely produces a whole host of fluids, not the least of which are diarrhoea, stoma output, drain fluid and vac dressing discharge, blood loss, not to mention sweat and the evaporative losses from the lung. So there is more to a negative fluid balance then just the urine output. However, that is the volume we can control the most directly, and measure conveniently, which is why we fixate upon it. Weight measurements are notoriously unreliable in the ICU, educated guesstimates are wildly inaccurate, and "dry" weight measurements are often unknown, which is why serial weights from the ICU bed are unlikely to be a good guide.

So, what should your endpoint be? Protocolised diuresis studies often fail to protocolise this specific aspect. For example, Bissell et al (2020) had their clinicians aim for -1000 to -3000 ml/day of negative fluid balance, but where along this continuum the actual target would be, and how that should be decided, was something they left to the discretion of the treating team. Similarly, the RADAR-2 trial protocol gives a range of -1000 to -3000 ml. The actual balance they achieved was - 860ml in the first 24 hrs, and because the investigators concluded with the confusing statement that their intervention *"may cause benefit or harm"* we can

deduce that that was not a clinically meaningful amount. Probably more is needed. According to meta-analysis by Messmer et al (2023), a lot of the other studies in this field are frustrated by a lack of study group separation, i.e. they did not find what they were looking for because the fluid balance effect of their intervention was insufficient. Most of these trials reported an integroup difference of about 1L per day. From this, we can infer that the fluid balance should be more negative than that. In fact, it may be that more negative is more better: the retrospective sepsis cohort from Dhondup et al (2020) had a sustained mortality reduction from each cumulative litre of negative balance.

But how much is too much? Nothing more scientific than a general vibes-based impression exists to guide this decision, in the vast majority of ICU patients. One is left with the pragmatic advice that a clinical assessment of the patient needs to give the impression that:

1. The patient's poor condition is due to fluid overload, according to various parameters such as the presence of peripheral and radiological oedema, and
2. The sustained diuresis is improving these parameters, and
3. The rate at which these parameters are improving is fast enough to permit the deescalation of support before that support becomes burdensome or causes complications

In short, the diuretic strategy is helping you get the patient off the ventilator, or wean their supplemental oxygen, or it is decongesting their heart in a way that improves their LFTs and decreases their inotrope requirements, and this is happening fast enough that the strategy should allow these supports to be weaned soon, before they start causing problems (VAP risk and CVAD infection risk increases with every day, for example), or before they become critically enfeebled by mechanical ventilation, or before you have to contemplate something invasive like a tracheostomy.

Why isn't it working?

"Resistance" to loop diuretics in the ICU is one problem, which is the loss of effect with sustained dosing that occurs in the course of chronic treatment. This is discussed well enough in the chapter on frusemide, and will not be repeated here, other than to mention that the main reason for this phenomenon is the upregulation of downstream sodium reabsorption capacity downstream from the site of loop diuretic action, which is a reflex response to volume loss and which

counteracts the diuretic effect. For most patients with chronic heart failure, this process is already in progress, and will go unnoticed by ICU staff, except in the occasional raised eyebrow at the total daily dose the patient usually requires in the community.

"Refractoriness" is a completely separate phenomenon. A dose, regarded by all to be formidable, is administered; and hours pass with no increase in the urine output. This is a much bigger problem.

The cause of this could be a whole host of reasons, such as:

- The kidneys are well and truly baked, and there is no dose of frusemide that could awaken them into action
- The cardiac output is too poor to wash any frusemide through the glomerulus
- The central venous pressure is so high that the transrenal pressure gradient is insufficient and renal blood flow is poor
- The patient is receiving so little salt in their diet and fluids that there is insufficient sodium delivery to the tubule, and therefore nothing for the frusemide to act on
- The albumin is so low that there is minimal delivery of frusemide to its site of action
- The patient is so uraemic that their accumulation of organic anion toxins is competing with frusemide for active tubular secretion by OATs in the proximal tubule

Or fifty other things. But perhaps you just haven't given *enough* frusemide.

When should I add another diuretic?

Or just keep going with increasing doses of the same one? *"A maximum daily dose of 1000mg should not be exceeded"*, warns the PI document, but since when does an intensivist listen to such advice? Frusemide dosing in ICU, in the hands of the motivated user, does seem extremely elastic, stretching well outside the comfort zone for most ICU pharmacists. The author's older colleagues once recalled seeing cardiologists prescribe 100mg/hr infusions, and one occasionally finds an article like Van Meyel et al (1994) who mentions a maximum dose of 160mg/hr, or De Bruyne et al (2003) who mentions 200mg/hr. This seems baffling

and surely must represent some kind of desperation (because what court of peers would defend this practice when the deaf patient takes you to court). Most reasonable people would do basically anything else. But this does raise the question: how high do you push the dose of the loop agent before you resort to adding another class of diuretic, and in which circumstances?

When a negative balance is not achieved by monotherapy

Logically, the answer to the question "when do I start a second agent" could lay anywhere along the continuum between "always, immediately" and "only when you have maxed out the dose of the first one". Both extremes seem somewhat farfetched, but the general, if the main objective is "more urine", then the trend among society guidelines and trials seems to be in the direction of the latter, i.e. diuretic combinations seem to be resorted to when the loop diuretic appears to be ineffective. As an example of this, in their 2022 heart failure guidelines the AHA recommend that a thiazide be added only *"for patients who do not respond to moderate or high-dose loop diuretics".* In the DOSE trial (Felker et al, 2011), where acutely decompensating patients were either continued on their usual diuretics or subjected to a 2.5×dose increase, there was no real adverse event problem to speak of, except for a trivial elevation of the creatinine; so perhaps "give more of the same" is the answer to this question.

How much more of the same? By reviewing the contemporary guidelines, and specifically the references they give in support of their low-grade "expert opinion only" recommendation, one can make a vague dose guide by looking at the loop diuretic doses mentioned by the mostly narrative reviews or observational studies they quoted (most of which were from the 1970s and 1980s). The only trial among them was Channer et al (1994), whose patients were on 160mg/24 hrs of IV frusemide.

In the DOSE trial there was no second agent used, but the loop diuretic dose that most patients ended up being safely escalated to was also something like 160-200mg per day. One may safely call a failure to respond to this dose "loop diuretic refractoriness", and reach for a second agent.

When do you decide that a negative balance is not enough? And by extension, how much diuresis is too much?

When you want to avoid the adverse effects of high dose loop diuretics

On the other hand, if the second agent is being contemplated because the loop diuretic is causing side-effects, then it is probably better to start it early, as the most notable side effects of the loop diuretic class are biochemical derangements which can be easily overcome with the addition of other diuretics, and would manifest themselves well before the 160mg/day threshold. This begs the question, why do we not exploit diuretic synergy more often? Most often the answer is embedded in the conservative (and usually correct) belief by intensivists that polypharmacy and care complexity are evil on some kind of fundamental moral level, and should be avoided. If you can solve a problem with one agent, and perhaps a handful of KCl ampoules, why would you overthink the choice of diuretics? Electrolyte replacement in the ICU is proactive, safe, and exposes the patient to no additional risk - it is telling that even the high-dose group in the DOSE trial had a trivial incidence (~1%) of serious adverse events from electrolyte derangement. This is probably the correct approach; to take a contrary position (that all diuretic therapy must be a combination of at least three if not four synergistic agents) increases the cost of care and exposes the patient to small but measurable risks which would accumulate with widespread adoption. The reader will note that this is not a very strong argument, and move on.

"Sequential nephron blockade"

The term "sequential nephron blockade" seems to appear for the first time in Puschett (1986), who used to describe the technique of blocking sodium reabsorption at several sites in the nephron simultaneously, using multiple diuretic agents. The term "sequential" here does not imply that one site is blocked before the next in some kind of graded escalation, but that consecutive nephron sites are blocked, leading to an amplification of diuretic effect. The author was mostly referring to adding a thiazide. That is also the meaning taken by most modern writers, even though their review articles inevitably have a table listing other diuretic classes, and/or a table listing synergistic combinations of two or more agents. Just adding a thiazide is not really much of an escalation pathway anyway, i.e. one step does not make a ladder; and it does raise an important point: you can use these drugs all together as a package, or you can gradually introduce them as they become relevant.

Block the whole nephron to begin with

Starting several classes of diuretics simultaneously is definitely an option. The downside of this is that it becomes difficult to predict exactly how much diuresis to expect, and one might be unpleasantly surprised by how much volume is lost. One would have to be reasonably confident that the strategy is not going to result in an embarrassing overshoot, kicking the kidneys while they are down.

Block the nephron slowly, site by site

The ladder of diuretic escalation can be loosely described as a series of reactions to the adverse electrolyte changes that occur with the use of loop diuretic monotherapy. What follows is an attempt to present the already excellent table from Frățilă et al (2023) in a simple childish reinterpretation:

So, the frusemide is causing problems

Problem	An answer in the form of a diuretic
Hypokalemia	Amiloride and spironolactone
Hypernatremia	Thiazide
Metabolic alkalosis	Acetazolamide
Not enough diuresis	All of the above, together
Still not enough diuresis	add an SGLT2 and/or a vaptan
STILL not enough diuresis	Hypertonic saline

The table may suggest that the complication must occur to justify the escalation, but in fact it makes no logical sense to wait for them, and some may argue that any sufficiently aggressive diuretic fusillade should consist of something like this, as it is usually happening in a patient who will not be tolerant of wild electrolyte fluctuations.

Of these, potassium and magnesium depletion is probably the most noxious, with levels below 3.5 mmol/L being associated with a hazard ratio of 3.14 for sudden cardiac death among acute heart failure patients (Aldahl et al, 2017) and a mortality risk ratio of 1.9 for magnesium concentration of less than 0.7 mmol/L (Upala et al, 2016). It is also usually the first most apparent complication, as the other problems (sodium concentration, alkalosis, or failure to achieve a satisfactory negative fluid balance) take some days to develop or be noticed. Thus, the first choice of co-agent with a loop diuretic is often a potassium-sparing agent.

Which potassium-sparing diuretic should I use?

Under what circumstances would an important outcome hinge on the choice of ENaC-annoying agent? Among the agents, spironolactone is the oldest and best studied, and has therefore amassed a wealth of data in support of its use, particularly where long term heart failure survival is concerned. RALES trial, etc. However, in the ICU, we are frequently too impatient to wait for the several days that its action requires, making amiloride a better choice. It was quick and convenient to compare their properties in this table:

	Spironolactone	Amiloride
Class	Mineralocorticoid receptor antagonist	ENaC channel blocker
Chemistry	Steroid lactone	Pyrazinoylguanidine
Routes of administration	Oral only	Oral only
Absorption	95% bioavailability, when taken with food	50% bioavailability, which is reduced when it is taken with food
Solubility	pKa 18.01; practically insoluble in water	pKa 8.67; sparingly soluble in water
Distribution	VOD= about 2L/kg; 90% protein bound	VOD = 5L/kg; 23% protein-bound
Target receptor	Aldosterone receptors everywhere (particularly in the collecting duct and distal convoluted tubule)	Amiloride and triamterene both bind to and inhibit the ENaC sodium channel in the collecting duct
Metabolism	100% of spironolactone is metabolised in the liver - some of the metabolites are active and have long half-lives	Does not undergo any hepatic metabolism
Elimination	Elimination of inactive metabolites is renal. Half-life of spironolactone itself is only 2-3hours, whereas the metabolites have half-lives of 10-12 hrs	All of the administered dose is cleared renally; half-life is about 6-9 hours
Time course of action	Some effect is seen withn 3-4 hours, but the maximum effect takes up to 2 days to develop	Peak activity is about 2 hours after administration; effect last about 24 hours

Mechanism of action	By decreasing the reabsorption of sodium via the ENaC channel, aldosterone receptor antagonists increase the loss of sodium. The increased sodium concentration in the lumen of the collecting duct creates a positive charge which repels potassium ions and therefore leads to potassium retention.	By decreasing the reabsorption of sodium via the ENaC channel, amiloride and triamterene increase the loss of sodium. The increased sodium concentration in the lumen of the collecting duct creates a positive charge which repels potassium ions and therefore leads to potassium retention.
Clinical effects	Decreased blood pressure and circulating volume, hyponatremia, hyperkalemia, metabolic acidosis (Type 4 RTA), hirsuitism and gynaecomastia (by cross-reactivity with other steroid receptors, eg. sex hormones)	Hyperkalemia, hyponatremia
Single best reference for further information	FDA PI data sheet	TGA PI data sheet

Of these properties, the most notable is the difference in metabolism and elimination. The cardiorenal syndrome patient will have extremely poor renal clearance of everything, and amiloride is renally eliminated, which means its half life could be up to 100 hours or longer. On the other hand, spironolactone is metabolised into long-lived active metabolites, some of which are also renally cleared, and one might make the argument that amiloride will rapidly improve its own clearance by helping facilitate the sort of vigorous diuresis that is required to reverse cardiorenal syndrome. So this may not be such an important caveat. Spironolactone takes some time (perhaps several days) to properly evolve into its full effect, which is unattractive to a critical care practitioner who is accustomed to drug effect onset being limited only by the arm-brain circulation time. Other choices (eg. eplerenone and finerenone) are mostly popular because of their lack of sex hormone crosstalk, which is less important in the ICU where the patient relationship is hopefully too short-lived to see the effects of spironolactone on secondary sexual characteristics.

However, neither spironolactone nor amiloride are going to do very much to the actual volume of the diuresis, except by enabling ever-larger doses of frusemide.

These agents act on the final stages of urine production, where all but 3% of the total sodium has already been reabsorbed, and so do not have a particularly robust diuretic effect on their own. And because their effect on sodium reabsorption is relatively small, the loss of water will still be greater than the loss of sodium, and the patient will gradually become hypernatremic and alkalotic.

Why would I add a thiazide?

There are two main reasons.

- **Because they gradually become hypernatremic.** This is not intuitive, because the mechanism of action of loop diuretics is to block the reabsorption of sodium, but in fact the loss of water and volume triggers such a defensive response from the RAAS that the net effect of diuresis is actually hypernatremia. Yes, a lot of this is an aldosterone-related effect, and yes the aforementioned potassium-sparing diuretics should be sparing potassium precisely by preventing this sodium reabsorption, but practically their effect on total sodium movement is slow to develop and clinically irrelevant unless heroic doses are used. Velat et al (2020) only found significant sodium effects with long-term doses of around 100mg of spironolactone, to give an idea. Moreover aldosterone is only part of the picture, as natriuretic peptides and other mechanisms also play a role, well described in papers like Ellison (2001) that discuss mechanisms of diuretic resistance. In short, there may be no recourse other than to use a thiazide. This seems to be effective: Cote et al (2021), on review of the MIMIC-III database, noted that the risk of hypernatremia was greatly reduced (OR = 0.69) when the patient had a thiazide as a second agent.
- **Because you want more diuresis.** Thiazides block sodium reabsorption by inhibition of the thiazide-sensitive NCC sodium /chloride cotransporter in the distal tubule. This transporter will be responsible for reabsorbing a large amount of the extra unreabsorbed sodium that would be getting delivered here from the thick ascending limb where the loop diuretic is working. Thiazides on their own are relatively feeble as diuretics because ordinarily they can only work on something like 10% of the total filtered sodium, most of it having been already reabsorbed by the NKCC2 channels, but if these channels are blocked, thiazides markedly increase the magnitude of the diuresis by allowing all of this sodium to drift away down the tubule. Jentzer et al (2010) lists studies that explored this empirically; many found the total

urinary sodium excretion doubled or tripled, and the diuresis increased to something equivalent to using a quadruple dose of the loop agent on its own.

Why, then, do we not just add a thiazide to the loop diuretic to begin with, and forget about the potassium-sparing agents? Well. Both the loop diuretic and the thiazide will be producing potassium depletion at an accelerated rate. The addition of amiloride or spironolactone to a loop diuretic is unlikely to do harm in terms of overvigorous diuresis or hyperkalemia, because *hypo*kalemia and insufficient diuresis were the main problem to begin with. On the other hand, the addition of a thiazide to a loop diuretic will produce hypokalemia and hyponatremia, both of which are unpleasant for all kinds of reasons. Cote et al (2021) found the odds ratios for these to be and 2.28 and 1.7, respectively. Michaud & Mintus (2017) found the addition of metolazone to frusemide doubled their potassium replacement requirements.

What's the evidence for this triple diuretic therapy? Minimal, for heart-failure-associated fluid overload; but at least somebody reported it. Jermyn et al (2013) offered their experience of two cases where they used:

- Frusemide infusion, 10-40mg/hr
- Spironolactone, up to 50mg tds
- Metolazone, 5-10mg bd

They also threw in tolvaptan, 15-30mg/day. The authors did not report the electrolyte replacement doses, noting only that these were "stable". The strategy resulted in a tremendous negative balance (-32 L for one patient, over 8 days). Outside of the realms of heart failure, Witoon et al (2019) did an RCT in peritoneal dialysis patients where 100mg of hydrochlorothiazide and 50mg of spironolactone was added to 1000mg of frusemide. A higher urine output was observed in this outpatient population, and no serious adverse events.

When is acetazolamide the answer?

Metabolic alkalosis definitely tends to develop in the course of loop diuretic or thiazide therapy in the process of all those aforementioned aldosterone-mediated effects. The use of ENaC blockers can ameliorate this to some extent, but slowly and incompletely - Cote et al reported a drop of serum bicarbonate by about 1mmol/L over 3 days. Acetazolamide, in turn, was associated with a drop of 3.5

mmol/L, which is much better if you are wanting to avoid the evils of metabolic alkalosis.

Does it also help the diuresis? Perhaps, but not by much. Because the proximal tubule effects of blocking carbonic anhydrase decrease the delivery of chloride to the thick ascending limb, the effects of loop diuretics could in fact *be decreased,* at least theoretically. Practically Verbrugge et al (2019) found little difference in total daily natriuresis. The ADVOR trial (Acetazolamide in Decompensated Heart Failure with Volume Overload, Mullens et al 2022) achieved a paltry 500ml difference in negative fluid balance over 48 hours by adding acetazolamide to a loop diuretic. In short, you will not be adding acetazolamide to your nephron blockade as a measure aimed at volume control - it is mainly there to treat the alkalosis, which some might regard as cosmetic biochemistry.

SGLT2 in the critically ill, as diuretics?

These agents are mostly responsible for an improvement in hospitalisation rates, more so than mortality, which begs the question whether they are any good if you are already hospitalised and also sick enough to be in ICU. They are usually withheld for patients with an acute kidney injury, but there is some data that they do not delay renal recovery, making them a potential choice in cardiorenal syndrome (which is where you might find yourself reaching for an agent that prevents you from having to dialyse the patient). On the other hand, most intensivists will be reluctant to add these agents to a multi-diuretic regimen. Without labouring their risks extensively, most reasonable people would agree that there are other safer options, and the generally accepted viewpoint is that these agents should really be started when the patient is about to be discharged home.

Hypertonic saline as a co-conspirator for effective diuresis

Yes, this old counterintuitive strategy is a known One Weird Trick (Nephrologists Hate It) to wring diuresis from obstinately unproductive nephrons. There is probably no better way to review this strategy than this excellent post by Josh Farkas, but the reader with a strong preference for the formal process of peer review will probably want to explore Gandhi et al (2014). In short, this technique relies on hacking the endocrinology of the RAAS and can be summarised as follows:

- Hypochloremia stimulates renin release and sodium retention, and so the addition of chloride as hypertonic saline should prevent this.
- Hypertonic saline should also volume-expand the intravascular space, also disabling the RAAS and moving fluid into position to be ultrafiltered by the nephron.
- Ergo, hypertonic saline can prevent some of the mechanisms of diuretic resistance
- Additionally, hypertonic saline may cause some renal vasodilatation and therefore improve diuresis, but this is counteracted by the decrease in renal blood flow as the result of tubuloglomerular feedback. Fortunately, frusemide appears to block this mechanism, according to He et al (1995), causing the renin secretion by the macula densa to be essentially independent of the chloride delivery.
- In this fashion, frusemide potentiates the diuretic effects of hypertonic saline.

But… does it really have diuretic effects? Do we not in fact use it in TBI in preference to mannitol mostly because it *lacks* significant diuretic effects? Reader, one might think that this therapy might be rolled out when you are failing everything else, but it does not seem to have been studied in those sorts of edge cases. Farkas quotes a paper by Wan et al (2017) in whose cohort some patients had a beneficial response to hypertonic saline (about an extra 1200ml negative fluid balance per day), and the effect was most prominent seen in those who failed the usual combination of frusemide and spironolactone; but all the patients were reasonably well for ICU. All had NYHA grade III symptoms, were in their sixties, and had modestly depressed LVEF (~45%). In short, it is not known exactly where this therapy sits in the ladder of escalation, or whether it is even worth trying, because, let's face it:

Why not just dialyse them

The insane biochemical contortions of the paragraphs above may lead the reader to the inaccurate conclusion that dialysis in fluid-overloaded patients is so evil that it must be avoided at all costs, even if this requires the use of ear-destroying doses of frusemide and loss of rapport with the hospital pharmacy. This is in fact not accurate. Consider:

- Diuretics don't seem to improve mortality in heart failure anyway (or in other fluid overload states, eg. in deresuscitation from sepsis)

- Diuretics have nontrivial side effects
- One of those side effects is renal failure
- Failure to control the fluid overload can also cause renal failure (eg. in the context of cardiorenal syndrome)
- If the concern is that dialysis will cause some degree of kidney injury of its own, the data does not support this (eg. Costanzo et al, 2007, randomised patients to be filtered or pickled in frusemide, and found no difference in the final creatinine)
- The rate of fluid removal can be vigorous, resulting in shorter ICU stay and more rapid return to normal function (Costanzo et al, 2005), without the electrolyte derangement that would accompany an equivalent volume of diuresis
- The risks of RRT or intermittent dialysis, such as transient haemodynamic instability and vascular access complications, are insignificant compared to the overall mortality and morbidity profile of severe heart failure. Moreover peripheral access ultrafiltration should largely alleviate the concerns about CVAD problems, and has been known about for many years now. You can even use 18G cannulas.

In short, these therapies have been compared in a number of different ways, and at the bottom line there appears to be a conclusion that ultrafiltration is basically similar to diuretics in terms of outcomes, has no lasting disadvantages, and is a convenient and controllable method of fluid removal. Then why it is reserved for only medically refractory cases of fluid overload? Well. One may point to the vascular access and the anticoagulation and again remind the reader that increased invasiveness and complexity of care is broadly undesirable when simpler measures may be similarly effective. More importantly, from the viewpoint of the breathless person in the hospital bed, it is much easier to tolerate diuresis and electrolyte replacement than the insertion of a vas cath followed by three days of keeping one's head in *exactly the right position* for CRRT. The intensivist's need for control over numbers does not supercede the patient's need to have fewer holes in their neck.

Previous chapter: Acetazolamide

Next chapter: Measurement of glomerular filtration rate and renal blood flow

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